ments, therefore, cannot be directed to the immediate points they raised, but must be transposed into reflections on the wider implications of their thesis.

The astute observations initiated by Herrick many years ago have permitted an improved recognition of the significant distinctions differentiating angina pectoris and coronary occlusion. The latter condition, with its graver import, is based upon coronary vessel damage, whereas the former arises, presumably, from sympathetic spasm. This underlying pathologic difference demands a correspondingly different therapeutic approach.

It is altogether likely that a number of circulatory disorders, in addition to angina pectoris, have their origin in the common denominator of sympathetic sensitization or hypertonus. One need but mention intermittent claudication, Raynaud's disease, certain forms of gangrene, perhaps essential hypertension, and autonomic imbalance with vasomotor instability, as familiar varieties of angiospasm.

In the attempt to ameliorate or alleviate these vessel tightenings, resort has been had to a great number of drugs capable of producing some degree of vasodilatation. From most of these, merely transient pharmacodynamic effects have been obtained. The results achieved by Nuzum and Elliott and their predecessors, to whom they refer, seem, in some instances at least, to be of a more durable character; perhaps because body substances are utilized of which there may be a lack, with restoration of a more normal circulatory mechanism.

In recent years effort has been redirected, both medically and surgically, to a more specific and profound attack on the transmission lines of the sympathetic system itself, or at certain power houses, such as the adrenals, which store and release some of the stimulating energies of the network. Surgeons have performed such daring and novel maneuvers as ganglionectomies, nerve resections, adrenal denervations, and even adrenalectomy, followed at times by spectacular relief. One need but cite the prompt and complete cessation of violent attacks of paroxysmal hypertension by removal of an adrenal paraganglioma (cases of Mayo, Pincoffs and Shipley, Porter and Porter).

After all, it may turn out that angiospastic states occur because of an undue ascendency of the adrenal medullary stimulant adrenalin, due to a deficiency of its normal antagonists such as the circulatory hormone of Frey (kallikrein) or the insulin-free pancreatic extract. Now that two separate and differing extracts have been prepared from the posterior hypophysis, and two (with the probability of two or three more) from the anterior pituitary, it would not be surprising if a third extract, in addition to trypsin and insulin, were established for the pancreas. Also, since the anterior pituitary-like substance obtained from human pregnancy urine and human placenta may not be different and separate hormones from the sex hormones obtained directly from the prehypophysis itself, but merely altered in transit from gland to urine, so is it not likewise conceivable that the insulin-free pancreatic extract and the circulatory-urine extract kallikrein may be one and the same, but that the latter has slightly different chemical and physiologic properties because of modifications during transit? Many substances undergo chemical change from their site of origin to site of elimination.

It is to be hoped that greater quantities of these circulatory hormones will be available, and that their potency may be increased so that adequate clinical data may be accumulated. The duration of potency must be ascertained. To this end each batch must be retested periodically. No doubt some of the failures from the use of the commercial preparations can be ascribed to loss of potency. It would be unfortunate if this promising therapy were prematurely abandoned. Further reports from Doctors Nuzum and Elliot, and others, will be awaited with interest.

HYPERPYREXIA BATHS AND EPILEPSY*

THE CHEMICAL AND PHYSIOLOGIC RESPONSES OF THE BODY TO HYPERPYREXIA BATHS, AND THEIR SIGNIFICANCE IN THE EPILEPTIC SYNDROME

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DISCUSSION *by Samuel D. Ingham, M. D., Los Angeles; H. Douglas Eaton, M.D., Los Angeles; Thomas G. Inman, M. D., San Francisco.*

THE therapeutic use of hyperpyrexia baths has received increasing attention during recent years. The present state of knowledge concerning the underlying mechanism by which disease processes are influenced has not advanced, however, much beyond that of the ancients, who empirically discovered the healing properties of hydrotherapeutic measures many centuries ago.

Modern clinicians have pointed out the specific value of this measure and have directed attention to the febrile response of the body to hot baths as having special therapeutic significance. Many facts of practical importance have been added to the subject by the observations of Mehrtens and Pouppirt.[1,2]

Investigation along chemical and physiologic lines has revealed that the protective adjustments set into motion within the body upon exposure to high environmental temperatures are of such a magnitude as to be detected without difficulty, and of a quality as to directly alter the state of functional activity of the nervous system. Objective evidence for the latter assumption is found in the frequently observed clinical signs of tetany and of major convulsive seizures in epileptics during the course of hyperpyrexia baths.

The present discussion will bring to mind briefly the more prominent disturbances in chemical and physiologic equilibrium instituted by hot baths, and will attempt to correlate these changes with their apparent effect upon the convulsive tendency in patients presenting the epileptic syndrome.

SYMPTOMATOLOGY OF HYPERPYREXIA BATHS

A definite train of subjective and objective symptoms develops upon exposure of the human body to high temperature environments. These have been studied and well described by a group of careful observers.[3 to 10] The appearance of frank tetany in a certain number of subjects, and of convulsive reactions in many cases of epilepsy and general paresis, has led to a search for a possible explanation of these phenomena. Other neurological findings have been elicited under the influence of hyperpyrexia baths, to the end that localization of central nervous system pathology has been accomplished in a few cases. Temporary psychic disturbances have also been observed. Currie [11] described the abnormal symptomatology developed in baths of 105 degrees Fahrenheit in 1797, and advised strongly against temperatures above 100 degrees Fahrenheit.

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With these preliminary observations in mind, thirty-six hyperpyrexia baths were investigated in a group of well-defined and pronounced cases of the epileptic syndrome. Fifteen per cent of the baths induced typical major seizures, all appearing between twenty and forty-five minutes after the beginning of the bath, during the period of maximum chemical and physiologic change.

The self-evident conclusion that patients presenting convulsive disorders are not at all times in a state of susceptibility to artificially induced seizures is of special scientific interest. Certain preparatory changes, usually expressed in terms of excitability, precede the sudden release of nervous energy in the seizure. It is important to understand the nature of these changes before the mechanism for convulsive reactions may be comprehended. There is some evidence to show that an inherited constitutional convulsive tendency forms the basis for the later development of convulsions, whether of endocrine, chemical or organic origin.[12]

The periodicity of epileptic seizures may be said to represent evidence of a changing or cyclic susceptibility of certain individuals to convulsions, developed upon the basis of metabolic, chemical, physiologic and other changes not thoroughly understood. Foerster[13] and Rosett[14] have shown that the induced alkalosis of pulmonary hyperventilation does not regularly elicit convulsions in well-known epileptic subjects. Along the same line, Brody and De Barenne[15] have demonstrated the inherent fluctuations in excitability of the cerebral cortex. It remained for Krasnogorski[16] to show the pronounced effect of chemical and metabolic factors upon cortical excitation and inhibition.

The close observation of a large number of patients presenting the epileptic syndrome furnishes one with convincing information regarding the wave-like fluctuations in the intensity of nervous excitability occurring in these patients. Clues of impending attacks are acquired at times from the prodromal aurae, but much more frequently, and at an earlier period, are furnished by abnormalities in vegetative function (autonomic nervous system) and augmented motor and psychic activity (cerebrospinal and cerebral systems).

PHYSIOLOGIC CHANGES

The physiologic responses to hyperpyrexia baths are chiefly of respiratory and cardiovascular nature. Under ordinary environmental conditions, the demands of the human organism for cooling are compensated for by pulmonary hyperventilation, augmented elimination of water from the skin (loss of heat by evaporation), and direct radiation and conduction of heat from the body surface.[17,18] Under the conditions of the bath, heat cannot be dissipated at the surface; and since the pulmonary avenue of escape of heat is inadequate, the body temperature rises in direct proportion to the temperature of the bath. The baths of the present series were conducted with uniform technique, and resulted in a mouth temperature of 105 to 106 degrees Fahrenheit in thirty to forty-five minutes.

During the pulmonary hyperventilation of the bath, excessive amounts of carbon dioxid are lost in the expired air, lowering the carbonic acid content of the blood and terminating in a pronounced disturbance in acid-base equilibrium. Alkalosis of severe grade is developed. As the bath is continued the level of carbon dioxid in the blood falls so low that the respiratory center is only periodically stimulated, and a Cheyne-Stokes type of breathing makes its appearance.[19,20]

With exposure of the body to external heat, extensive peripheral vasodilatation is reflexly developed.[21,9,22,23,7] The sudden widening of the vascular bed and the consequent fall in peripheral resistance, as observed in greatly lowered diastolic pressure values, calls for cardiac and blood volume adjustments to insure the continuance of adequate circulation of the blood. The rate and the force of the heart beat are greatly increased, as reflected in the rapidly rising pulse rate and systolic pressure level. Blood volume increases by hemodilution of 10 per cent for the dual purpose of filling the greatly dilated vascular bed, and of bringing a greater volume of blood to the surface of the body for dissipation of heat through the evaporation of the sweat, as well as for direct radiation and conduction of heat from the surface.[17,18]

In addition to these changes, Mehrtens and Allred[24] have studied the intracranial pressure changes during hyperpyrexia baths. With rising increments of body temperature, the intracranial pressure was found to increase steadily.

In summary, the physiologic adjustments to hot baths have a less apparent and less direct influence upon nervous excitability than those of a chemical nature; nevertheless, those changes which have an activating effect upon the convulsive tendency are, in the light of recent research, the water shifting and the altered intracranial pressure relationships.

CHEMICAL CHANGES

The acid base shift of hyperpyrexia baths may be universally demonstrated in rising p_H values.[25,26,27,10,28] The ultimate pronounced grade of alkalosis follows the loss of carbon dioxid or carbonic acid from the blood (acapnia) during attempted cooling of the body by pulmonary hyperventilation.[29,30,20,31,5,25,18,6,7,9,10] The uncompensated carbon dioxid deficit thus established, by influencing the dissociation of oxyhemoglobin, causes the development of a state of functional anoxemia within the body.[32] The coexistence of alkalosis and anoxemia has given rise to a controversy of many years standing: it is generally agreed that augmentation of nervous excitability develops during hyperpyrexia baths, but a difference of opinion exists in assigning the cause to the alkalosis *per se*[33,34,35,32,9,10] or to the functional anoxemia.[31,20,36,6,37,38,21,32,28,7]

With these changes in nervous function in mind, further chemical studies have been made (unpublished data). In correspondence with Barbour's observations,[17,18] blood dilution of 10 per cent was demonstrated at the peak of body temperature. Blood sugar values declined roughly 10 per cent.[4,6,10,18,26] Diffusible and total serum calcium

analyses revealed a steady downward trend which, although not great, was, nothwithstanding, significant. The reciprocal relationship between calcium and inorganic phosphorus was born out by the rising serum inorganic phosphorus values.

Despite the presence of blood dilution, the albumin and globulin serum protein fractions were found to increase, owing to the influx of tissue proteins into the blood during the water-shifting.[39,40,18,41] The sodium chlorid content of the blood was not appreciably altered, indicating a balanced equilibrium between the tissue fluid and the blood.[42,43,44]

A review of the literature dealing with the influence of blood chemical conditions upon nervous excitability shows that states of alkalosis, anoxemia, hypoglycemia, low diffusible calcium and high inorganic phosphorus content of the blood, have a stimulating action upon nervous tissue. Furthermore, the recent work of Hodskins and his co-workers [45] has shown blood dilution to be associated with the active phases of the epileptic syndrome.

It could be said that the qualitative chemical changes established within the body under the influence of hyperpyrexia baths possess a uniformity of action upon nervous tissue, and in combination exert a pronounced augmenting effect upon nervous excitability.

SUMMARY

The effect of hyperpyrexia baths upon the human organism, then, is one of augmentation of cellular excitability developed upon the basis of alterations in chemical and physiologic equilibrium. The present discussion has been confined to these changes as they concern the functional activity of the nervous system. By the use of this measure, latent neurologic and psychic abnormalities have been made apparent.

The experimental use of hyperpyrexia baths in the study of convulsive disorders has been of practical value in the localization of the central pathology, and has shifted some of the clinically functional cases into the organic group. One outstanding example comes to mind of an adolescent girl who, after investigating the nature of her symptoms and in the absence of positive neurologic findings, was classified as a functional case. A major convulsive seizure was elicited by the bath and unquestionable unilateral localizing signs were brought out. Subsequent encephalographic study after lumbar air injection confirmed the localization and revealed an extensive unilateral atrophy of the cerebral cortex.

In view of the percentage (15 per cent) of hyperpyrexia baths resulting in convulsive reactions in well-known cases of the epileptic syndrome, it should be borne in mind that failure to induce a seizure does not rule out the possibility of epilepsy, while positive results are not only of diagnostic value, but frequently lead to the localization of the lesion.

Because of the property possessed by high temperature baths of augmenting nervous excitability, and of transposing latent into manifest neurologic signs, this experimental method can be offered for the study and diagnosis of a wide variety of disorders of the nervous system. The experimental investigation of the changes effected within the body by hyperpyrexia baths should lead to a better understanding of excitability, and to the discovery of the mechanism for the beneficial influence of fever therapy upon specific disease conditions.

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DISCUSSION

Samuel D. Ingham, M. D. (1253 Roosevelt Building, Los Angeles).—There is slow but definite progress in solving the problems of epilepsy, and what is more important, progress is being made in the obscure field of biochemistry. It has been fairly well established that varying concentrations of many different substances in the blood stream can be correlated with varying degrees of excitability in the central nervous system, and to a certain extent with the incidence of convulsions in those suffering from epilepsy. There is much evidence to indicate that the threshold for convulsions is lowered when the blood contains a low amount of diffusible calcium, sugar, and carbon dioxid. On the other hand, a high content of inorganic phosphorus and potassium likewise causes nervous irritability. A water balance in the tissues also appears to be a matter of importance. We have a rather vague conception of the existence of many other factors acting as so-called toxic agents, some of endogenous origin as indicated by the eclamptic and uremic states, and also exogenous substances of infinite variety. In general it may be stated that the whole problem resolves around the integrity and the functional activity of the nerve cells, singly or collectively, particularly as the cells are influenced each by its immediate environment, consisting of fluid derived from the blood containing varying amounts of many different chemical elements in varying combinations. The physical conditions influencing the functional activity of the cells include not only the chemical content of the fluid surrounding it, but the varying conditions of surface tension, electrolytic balance, colloid state, and other physical conditions. It will take a long time for science and research to correlate all of the facts that can now only be barely visualized. Doctor Hopkins' series of observations on epileptics who are given hyperpyrexia baths is another step in the direction of evaluating the changes induced by this procedure. No claim is made that it is a useful therapeutic measure, but valuable information may be obtained, especially in the way of diagnosis in cases of organic cerebral disease without manifest localizing symptoms. If by means of hyperpyrexia localizing symptoms of organic disease may be made manifest, the measure becomes an important diagnostic procedure in selected cases.

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H. Douglas Eaton, M. D. (1136 West Sixth Street, Los Angeles).—Recent studies of epilepsy have not only added to our knowledge of the mechanism of convulsive seizures, but have provided us with practical aides in the treatment of this distressing disorder. Doctor Hopkins' excellent presentation of her painstaking observations on the physiological and chemical changes occurring in epileptics during hyperpyrexia baths is of definite value from the standpoint of etiology and diagnosis.

It is of interest to note that in spite of proved changes in water balance and in intracranial pressure, as well as the production of alkalosis and functional anoxemia, only 15 per cent of the baths produced seizures in a group described as showing well-defined and pronounced epileptic syndromes. These observations remind us again that we are still confronted with an unexplained and important factor in the genesis of convulsive seizures—the so-called convulsive tendency noted by Doctor Hopkins and other observers. The physiologic and chemical factors, such as alkalosis, anoxemia, and disturbances in water balance, act as excitants of this inherent latent hyperexcitability of the central nervous system. Further studies should yield us further practical help in the clinical handling of epileptics.

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Thomas G. Inman, M. D. (2000 Van Ness Avenue, San Francisco).—In this paper the author presents the results of carefully conducted studies. The hyperpyrexia bath has enabled her to investigate the effects of temperature elevation in epileptics and to make such deductions from her findings as, in her experience, seemed warranted.

If the bath does nothing more in these cases than induce an attack in the presence of a trained observer, it would be a valuable aid to clinical investigation. Strange as it may seem, the physician seldom sees the convulsions he is called upon to treat; and since many convulsive attacks bear no relationship to epilepsy, the opportunity to observe a seizure may lead to a revision of opinion and point the way to curative therapy.

Epileptoid attacks can be induced in some individuals in a number of ways. It is a matter of clinical observation that certain individuals exhibit more or less mental disturbance, with increase in body temperature, and in children of the nervous type any febrile condition may be initiated by a convulsion. But this is not epilepsy.

In any consideration of the epilepsy problem it must be kept in mind that the generalized convulsion is but a motor cortex response to something which precedes it. Is it the unconsciousness, which seems to be an essential feature of the disease, or something initiated during that period that, acting through the circulation, sets the motor cells into action?

Or does the epileptic possess an easily excitable cerebral cortex, which occasionally reacts in this special manner to sudden variations, however induced, in circulatory balance? Epileptoid seizures can be brought about by inducing an arteriovenous capillary stasis, and it is not unlikely that this phenomenon is responsible for no small number of the secondary epilepsies. It is, however, not easy to explain the character of the epileptic and the numerous epileptic equivalents on these grounds.

Whatever the ultimate answer to the problem may be, Doctor Hopkins has added to the positive knowledge relating to the body chemistry of these unfortunates for which all interested are duly thankful.

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Doctor Hopkins (Closing).—I am grateful for the comments made upon the subject material of the above paper. It becomes very evident that we are still dealing with surface phenomena, and have not penetrated far into the actual conditions developed within the central nervous system structures in preparation for convulsive reactions. The experimental and clinical methods in use today appear the more crude and ineffective when confronted with the necessity for understanding the mechanism of convulsions. We must ultimately know more about the individual cellular unit and the environmental conditions which influence its functional activity.